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Propolis and growth factors in wound healing: friends or foe?

Skin wound healing is a vital process that is important for re-establishing the epithelial barrier following disease or injury. Aberrant or delayed skin wound healing increases the risk of infection, causes patient morbidity, and may lead to the formation of scar tissue. The long history of bee domestication has led to an exploitation of bee products, and the many favorable properties of propolis lend to its application in many human pursuits. Propolis is as old as honey, and man has used it for ages. Today, the long history of the use of propolis continues in home remedies and personal products.

Propolis, or bee glue, is a natural wax-like resinous substance found in beehives where it is used by honeybees as cement and to seal cracks or open spaces. Bees use propolis not only as a building material, but also to keep low concentration of bacteria and fungi into the hive. Along with other honeybee products (honey, royal jelly, pollen), propolis has great therapeutic properties, being used since antiquity in popular medicine in various parts of the world. Propolis is believed to have antiseptic, antibacterial, antimycotic, astringent, spasmolytic, anti-inflammatory, anaesthetic, antioxidant, antifungal, antiulcer, anticancer, and immunomodulatory effects. Although its chemical composition varies, propolis constituents generally include about 10% essential oils, 5% pollen, and 15% various organic polyphenolic compounds. However, despite the numerous studies conducted so far, little is known about the cellular and molecular mechanisms involved in propolis-promoted wound healing. Therefore, it requires further research that may lead to new discoveries of its composition and possible application.

So, we propose to study wound mechanisms *in vitro* by exploring propolis effects on single skin cell types, such as keratinocytes and fibroblasts, and on the whole tissue by using a 3D skin model. These effects will be studied through *in vitro* scratch wound and cell migration assays, coupled to light microscope image analysis.

In fact, growth factors have significant, positive actions during the wound healing process. Some of these factors have also important action on extracellular matrix remodelling. However, excess growth factor presence or activity can produce pathological changes during wound repair, such as fibrosis or keloid formation. The behaviour of some biomolecules, such as growth factors and cytokines, will be studied during wound healing in presence of propolis. Our idea is to test if propolis

can act synergistically with growth factors or if propolis can reduce negative effects of growth factors on wound healing.

Particularly suitable biomolecules will be, for example, platelet derived growth factor (PDGF), transforming growth factor beta (TGFβ), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), human growth factor (HGF), bone morphogenetic proteins (BMPs), insulin-like growth factors (e.g., IGF-1 and IGF-2), keratinocyte growth factor, various macrophage and monocyte mediators such as tumor necrosis factor α (TNFα), interferon gamma (IFNγ), and granulocyte-macrophage colony stimulating factor (GM-CSF), and combinations thereof. Suitable cytokines can be, for example, interleukins (e.g., IL-1-IL-36) and interferons (e.g., interferon type I, interferon type II, interferon type III).